REMARKS:

I. Status of the Claims

Claims 11-47 are pending, with claims 12, 16, 20, 21, 25, 28, 32, and 34 being withdrawn for being directed to non-elected species. By this amendment, claims 1-10 are canceled without prejudice, claims 11 and 24 are amended, and new claims 39-47 are added. The claim amendment and new claims do not add new matter and are supported by the specification.[1]

II. 35 U.S.C. § 103 Rejections

Reconsideration is respectfully requested of the rejection of claims 11, 13-15, 17-19, 22-24, 26, 27, 29-31, 33, and 35-38 under 35 USC § 103(a) in view of Reed et al. (US 6,727,356) and Nikiforov et al. (US 6,777,184).

(a) claims 11, 13, 14, 15, 17, 18, 19, 22, and 23 are not rendered obvious by the cited art

Claim 11, as amended, is directed to a method for detecting or quantifying a nucleic acid analyte that requires a nucleic acid probe comprising 1) monomeric LNA moieties, wherein the ratio of LNA moieties to standard nucleic acid moieties is from about 1:5 to about 1:1.4, and 2) two or more non-identical covalently attached dyes, wherein at least one dye is fluorescent. Typically, a probe required in claim 11 will comprise two or more LNA moieties. For example, a 12 nucleotide long probe could comprise 2 LNA moieties and 10 standard moieties, 3 LNA moieties and 9 standard moieties, 4 LNA moieties and 8 standard moieties, or 5 LNA moieties and 7 standard moieties.

As correctly noted by the Office,[2] Reed et al. fail to disclose nucleic probes comprising LNA moieties. Rather the probes of Reed et al. have covalently attached non-identical dyes (i.e., fluorescent and quencher dyes).[3] The disclosure of Nikiforov et

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[1] Support for the amendments to claims 11 and 24 may be found, for example, in published paragraph [0080] and Table 1 of the pending application. Support for new claims 39-41 may be found in published paragraph [0080] and Table 1 of the pending application. Support for new claims 42-47 may be found in published paragraphs [0065], [0080], [0083] and Tables 1 and 3 of the pending application.

[2] See Office action dated 10/25/10 at page 4, line 8.

[3] Reed et al., at column 5, lines 17-20.

al. fails to supply the deficiencies of Reed et al. as a reference. Nikiforov et al. do not disclose nucleic probes comprising LNA moieties in which the ratio of LNA moieties to standard moieties ranges from about 1:5 to about 1:1.4, as required in claim 11. Rather, the Nikiforov et al. reference discloses "a probe nucleic acid comprising a PNA (or a DNA, LNA, or RNA, etc.), e.g., comprising a rhodamine label."[4] The Office states that it "would have been prima facie obvious to one of ordinary skill in the art at the time of the invention was made to use the LNA moiety, as taught by Nikiforov et al. with the probes as taught by Reed et al."[5] The combination suggested by the Office, however, would not arrive at the probe required in the method of claim 11. Neither reference, when taken singly or collectively, discloses or suggests using a LNA-containing probe in which the ratio of LNA to standard moieties ranges from about 1:5 to about 1:1.4, as required in claim 11. Thus, the cited references fail to disclose or suggest all of the required claim elements. Moreover, neither the cited references nor knowledge available to those skilled in the art provided sufficient guidance to modify the probes of Reed et al. and arrive at the LNA containing probes required in claim 11 with a reasonable expectation of success. Rather, the Applicants undertook significant trial and error testing to determine the optimal design of the probes required in claim 11.

The Office states that an "ordinary practitioner would have been motivated to use LNA moiety . . . in order to have probes with higher avidity, affinity and/or specificity that corresponding standard DNAs …."[6] Although Nikiforov et al. disclose that "LNAs can often bind to DNAs or other nucleic acids with higher avidity, affinity, and/or specificity than corresponding standard DNAs,"[7] this reference fails to recognize that the ratio of LNA moieties to standard moieties is important. The Applicants discovered that probes having a ratio of LNA to standard moieties ranging from about 1:5 to about 1:1.4 had significant advantages over other probes. For example, the Applicants *surprisingly discovered* that the overall length of a probe could be decreased if the LNA content was increased. Example 4 of the pending application details experiments in which the effectiveness of different length probes with different numbers of LNA moieties was analyzed. It was discovered that 13 nucleotide-long probes having 5 LNA moieties (i.e.,

[4] Nikiforov et al., at column 7, lines 40-42.
[5] Office action dated 10/25/10, at page 4, last paragraph.
[6] *Id.*, bottom of page 4 to top of page 5.
[7] Nikiforov et al., at column 7, lines 4-7.

probe pair 5) were as effective and specific as 17 nucleotide-long probes having 3 LNA moieties (i.e., probe pair 2) in discriminating between wild type (I), heterozygous (II), and mutant (III) target sequences (compare FIG. 1E with FIG. 1B). Discovering that probes could be made shorter by increasing the number of LNA residues is significant because the cost of making the probes could be reduced. For example, synthesizing shorter probes requires fewer nucleotide building blocks, as well as reduced amounts of catalysts, blocking groups, co-reactants, solvents, etc. Additionally, the amount of hazardous chemical waste would be reduced. Thus, besides increased specificity or effectiveness, LNA-containing probes can be made shorter, thereby reducing costs and chemical wastes.

The Applicants also discovered that LNA moieties could be situated in any position of a nucleic acid probe.[8] In particular, a LNA moiety "positioned opposite to the SNP site subsequent to the hybridization of the probe with the analyte"[9] differentiated between wild type (I), heterozygous (II), and mutant (III) target analytes much better than probes lacking LNA moieties (compare FIGs. 1B-1E with FIG. 1A). The Office states that "Nikiforov et al. teach nucleic acid probes derivatized with fluorescent dyes which also comprise monomeric LNA moieties and the LNA moiety is complementary to the opposing SNP site subsequent to the hybridization of the probes with the target analyte (see col. 7 lines 40-41, where a probe is disclosed with contains a rhodamine label and a LNA moiety and col. 13 lines 50-67, where SNP is disclosed)."[10] This interpretation not correct, however. While Nikiforov et al. discuss LNA probes in col. 7 lines 40-41 and discuss SNP in col. 13 lines 50-67, *nowhere does this reference disclose or suggest preparing or using probes containing a LNA residue opposite the SNP site as concluded by the Office*.

In summary, the cited references fail to disclose or suggest using LNA-containing probes having a ratio of LNA to standard moieties that ranges from about 1:5 to about 1:1.4, as required in claim 11. Additionally, neither the cited references nor knowledge available to a skilled artisan provided sufficient guidance to modify the probes of Reed et al. as suggested by the Office to arrive at the LNA containing probes of claim 11 with

[8] Pending application at published paragraph 0026.
[9] Id., at published paragraph 0066.
[10] Office action dated 10/25/10, at page 4, lines 13-17, emphasis added.

a reasonable expectation of success. Thus, Applicants respectfully submit that claim 11 is not *prima facie* obvious. Claims 13-15, 17-19, 22, and 23, which depend from and incorporate all the limitations of claim 11, likewise are not obvious in view of the cited art for the same reasons stated above with respect to claim 11.

In view of the above, the Applicants respectfully request withdrawal of the § 103 rejections of claims 11, 13-15, 17-19, 22, and 23 in view of Reed et al. and Nikiforov et al.

(b) claims 24, 26, 27, 29, 30, 31, 33, 35, 36, 37, and 38 are not rendered obvious by the cited art

Claim 24, as amended, is directed to a method for detecting or quantifying a nucleic acid analyte that requires a pair of nucleic acid probes that differ in their nucleic acid sequences and collectively comprise 1) monomeric LNA moieties, wherein the ratio of LNA moieties to standard nucleic acid moieties in a LNA-containing probe is from about 1:5 to about 1:1.4, and 2) two or more non-identical covalently attached dyes, wherein at least one dye is fluorescent and each probe comprises at least one of said dyes.

Claim 24 is not obvious in view of Reed et al. and Nikiforov et al. for the same reasons articulated above in section (II)(a) with respect to claim 11. The cited references fail to disclose or suggest using LNA-containing probes in which the ratio of LNA moieties to standard nucleic acid moieties ranges from about 1:5 to about 1:1.4, as required in claim 24. Additionally, neither the cited references nor knowledge available to one skilled in the art provided sufficient guidance to modify the probes of Reed et al. as suggested by the Office to arrive at the LNA containing probes of claim 24 with a reasonable expectation of success. Accordingly, it is respectfully submitted that the claim 24 is not *prima facie* obvious. Claims 26, 27, 29-31, 33, and 35-38, which depend from and incorporate all the limitations of claim 24, likewise are not obvious in view of the cited art for the same reasons articulated above with respect to claim 24.

In light of the foregoing, it is respectfully requested that the § 103 rejections of claims 24, 26, 27, 29-31, 33, and 35-38 in view of Reed et al. and Nikiforov et al. be withdrawn.

III. New Claims 39-47 are Novel and Non-Obvious

New claims 39-41, which depend from and incorporate all the limitations of claim 11, are novel and not obvious in view of the cited art for the same reasons stated above in section (II)(a) with respect to claim 11. Neither Reed et al. nor Nikiforov et al. disclose or suggest LNA-containing probes having the required number of LNA and standard nucleic acid moieties recited in claims 39-41.

New claims 42-47, which depend from and incorporate all the limitations of claim 24, are novel and non-obvious in view of the cited art for the same reasons stated above in section (II)(b) with respect to claim 24. Neither Reed et al. nor Nikiforov et al. disclose or suggest using a pair LNA-containing probes having the required number of LNA and standard nucleic acid moieties (as recited in claims 42-44) or a pair of probes in which one has the required number of LNA and standard nucleic acid moieties and the other has no LNA moieties (as recited in claims 45-47).

IV. Conclusions

In light of the foregoing, the Applicants request entry of the claim amendments and new claims, withdrawal of the claim rejections, and solicit an allowance of all pending claims. The Examiner is invited to contact the undersigned practitioner should any issues remain unresolved.

Respectfully submitted,

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